Patent
Attorney's Docket No. 1033172-000001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	**MAIL STOP AF**
Elisabeth Wolpert et al.	)	Group Art Unit: **1643**
Application No.: 09/319,736	)	Examiner: KAREN A CANELLA
Filing Date: August 2, 1999	)	Confirmation No.: 3510
Title: THERAPEUTIC APPLICATIONS OF ANTIGENS OR EPITOPES ASSOCIATED WITH IMPAIRED CELLULAR PEPTIDE PROCESSING, E.G. EXPRESSED ON RMA-S CELLS TRANSFECTED WITH A B7-1 GENE	)	

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s). (Note: no more than five pages are provided.)

Respectfully submitted,

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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Claim rejection under 35 U.S.C. § 102(b):

Claims 143-147, 159 and 162 were rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Nair et al. (U.S. Patent Number 5,831,068). This rejection has been obviated by an amendment pursuant to 37 C.F.R. § 1.116 previously filed by applicants. The prior filing of an amendment to obviate a rejection does not preclude the filing of this request pursuant to New Pre-Appeal Brief Conference Pilot Program, O.G. (12 July 2005). The present request addresses the remaining three rejections, which applicant respectfully submits are improper for at least the following reasons.

Claim rejection under 35 U.S.C. § 102(b):

Claims 155-157, 160 and 161 have been rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Hammond et al. (Nature, 364:158-161, 1993). Hammond et al. does not anticipate the claimed invention.

Tumor metastasis frequently relies on impaired MHC presentation to permit the tumor cells to avoid recognition and attack by the immune system. The novel methods of the present invention are directed to a process for isolating immunological effector cells that selectively recognize cells showing impaired cellular peptide processing for MHC presentation, and cells that induce such selective recognition in activate CD8+ T lymphocytes. Prior to the discovery by the present inventors, it was not known or even believed that it would be possible to induce immunological effector cells that selectively recognize cells showing impaired cellular peptide processing for MHC presentation.

The method of the present invention results in the isolation of immunological effector cells that selectively recognize cells showing impaired cellular peptide processing for MHC presentation. Hammond et al. does not teach a method that accomplishes this result.

Hammond et al. did not treat cells in vitro with an effective dose of a substance that impairs cellular peptide processing for MHC presentation or isolate cells which activate CD8+ T lymphocytes that selectively recognize cells showing endogenous epitopes associated with impaired cellular peptide processing for MHC presentation as required by the methods of claim 148 and claim 155. Hammond et al. expressed *env* and gp120 from HIV in T2 cells, which have a TAP-1 and Tap-2 knockout deletion. Hammond et al. found that is was possible for CD8+ CTL specific for the HIV protein epitopes to lyse T2 cells expressing gp120 even in a TAP defective background. Not having isolated any cells which meet the requirements of claim 148, Hammond et al. did not teach or suggest combining such cells, or

antigens, or epitopes expressed by such cells with a pharmaceutically acceptable additive as required by claim 160.

Hammond et al. did not stimulate immunological effector cells in vitro with cells which activate CD8+ T lymphocytes that selectively recognize cells showing endogenous epitopes associated with impaired cellular peptide processing for MHC presentation as required by the method of claims 155-157. CTL that Hammond uses in their assay methods were specific for HIV epitopes and were not directed to endogenous epitopes.

Therefore, Hammond et al. did not perform, teach, or even suggest a method as recited in claims 155-157. Not having isolated any isolating immunological effector cells that selectively recognize cells showing impaired cellular peptide processing for MHC presentation, Hammond et al. could not teach or suggest a composition comprising such cells as required by claim 161.

Hammond et al. did not anticipate the present invention, and the rejection should be withdrawn.

Claim rejection under 35 U.S.C. § 103(a):

Claims 148-158, 160 and 161 have been rejected under 35 U.S.C. § 103 as allegedly unpatentable over Nair et al., (U.S. Patent Number 5,831,068), in view of Sandberg et al. (Eur Journal of Immunology, 26:288-93, 1996) and Skipper et al. (J. Experimental Medicine, 183:527-34, 1996). Applicants maintain that the rejection has been traversed.

The prior art fails to establish a proper prima facie case of obviousness. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. § 2143.

The object of Nair et al. is to provide an efficient means to prepare cells that present an **exogenous** epitope of interest in place of the peptides that would be normally presented. Nair et al. is not concerned with and did not teach or suggest isolating cells which activate CD8+ T lymphocytes that selectively recognize cells showing endogenous epitopes associated with impaired cellular peptide processing for MHC presentation. Nair et al. only prepares cells that present exogenous epitopes.

Nair et al. teaches treating cells with a substance that impairs cellular peptide processing for MHC presentation for a purpose that is in opposition to the presently claimed

methods. Neither Sandberg et al or Skipper et al. suggest treating cells with a substance that impairs cellular peptide processing for MHC presentation.

Sandberg et al. studies the CD8+ CTL population in TAP1 defective (-/-) mice. Sandberg et al. did not teach or suggest that the CD8+ CTL of TAP1 defective mice was selective for cells showing endogenous epitopes associated with impaired cellular peptide processing for MHC presentation and did not suggest isolating such cells.

The Office alleges that Skipper et al. teaches that post translation modification can lead to generation of new antigens which are relevant to tumor rejection. However, this does not suggest any of the steps of the presently claimed methods.

Nair et al. did not appreciate and did not suggest that it would be possible to isolate cells which activate CD8+ T lymphocytes that selectively recognize cells showing **endogenous** epitopes associated with impaired cellular peptide processing for MHC and doing so would be contrary to the purpose of Nair et al. None of Nair et al., Sandberg et al. or Skipper et al. teach or even suggest isolating cells which activate CD8+ T lymphocytes that selectively recognize cells showing **endogenous** epitopes associated with impaired cellular peptide processing for MHC presentation as required by claim 148.

Therefore, the combination of Nair et al., Sandebrg et al., and Skipper et al. fails to even suggest all the steps of claim 148 of any claim dependent thereon.

Furthermore, there could not have been any motivation to modify Nair et al. as the Office has proposed, because the proposed modification would have been contrary to the purpose of the teaching of Nair. If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Nair is directed to a method of preparing cells presenting **exogenous** epitopes of choice, the very idea of isolating cells which activate CD8+ T lymphocytes that selectively recognize cells showing **endogenous** epitopes associated with impaired cellular peptide processing for MHC presentation would have been contrary to the object of the method of Nair et al.

Moreover, the combination of Nair et al. with Sandberg et al. and Skipper et al. does not suggest the insight necessary to provide a reasonable expectation of success in modifying Nair to arrive at the present invention. The finding by Sandberg et al. that TAP1 (-/-) mice possesses a diverse CTL response and the hypothesis of Skipper et al. that post translation modification can lead to generation of new antigens which are relevant to tumor rejection do not suggest that it would be possible to isolate cells that would induce a **specific** CTL

response to **endogenous** epitopes of cells with impaired cellular peptide processing for MHC presentation.

Thus, none of the requirements of a prima facie case of obviousness have been satisfied by the prior art, and this rejection should be withdrawn.

Claim rejections under 35 USC § 112:

Claims 155-157, 160, 161 and 164 have been rejected under 35 U.S.C. § 112 for allegedly failing to comply with the written description requirement. Applicants maintain that the rejection has been traversed.

The Office has previously asserted that the methods of claims 155-157 rely upon the cells isolated according to the method of claim 148. The Office has alleged that the cells that are isolated by the method of claim148 are not adequately described. In making this rejection, the Office implies that no process of manufacture can ever be sufficiently described if the process comprises the production of a novel intermediate material that is defined by its method of manufacture. This cannot be so. The Office has cited no authority that supports such a proposition.

The Office now asserts that the cells isolated in claim 148 rely upon treatment with a "substance" that is not adequately described. The Office alleges that claim 148 is a method of screening for the "substance." This is simply incorrect. Moreover, it is noted that the Office has acknowledged that the method of claim 148 (including all the elements thereof) is adequately described, as claim 148 has not been included in the present rejection.

A wide variety of representative examples of substances characterized in that tumor cells treated with the substance are subject to specific lysis by CTL elicited by endogenous MHC class I dependent antigens of the TAP-deficient variant of said tumor cell which has been transfected with the stimulatory molecule B7-1 as recited in claim 148 are described in the specification at page 8. Therefore, the Office is simply wrong to assert that method of claim 148 amounts to a method of screening for the "substance." The principles underlying the recited function of the substance and a representative number of examples of substances possessing the recited function are described in the specification so that a person of ordinary skill in the art would recognize that the inventors were in possession of the method of claim 148.

Claim 148 defines a process of manufacture. The cells isolated by the method of claim 148 have distinctive properties that are described in claim 148 by their selective induction of a specific immune response. The Office has not adduced any basis to doubt that the steps of claim 148 can produce isolated cells having the properties recited in claims 148.

Such a claim is analogous to claims to antibodies, including those yet to be isolated, which are held to be adequately described if the corresponding antigen is fully described. *See, Noelle v. Lederman*, 69 USPQ2d 1508 (Fed. Cir 2004). Antibodies are described by functional properties, which are a result of the process by which they are made. Here, the cells isolated by the method of claim 148 are described both in terms of the method of making the cells and by the ability of the cells to induce a specific response from immune effector cells.

Claim 155 is directed to an extension of the method of claim 148 which takes the product of claim 148 as an intermediate material and produces other isolated cells. Claim 157 is a product-by-process claim directed to a composition comprising such cells. Claim 155 and the claims that depend from claim 155 simply utilize the product of the method of claim 148 in further processing steps that result in a further related product that is, itself, defined by the process used to make it. Claim 161 is directed to a composition comprising the product of claim 155.

Product by process claims are proper under 35 U.S.C. § 112. *See, e.g.*, M.P.E.P. § 2173.05(p); *see also, In re Luck*, 476 F.2d 650, 177 USPQ 523 (CCPA 1973); *In re Pilkington*, 411 F.2d 1345, 162 USPQ 145 (CCPA 1969); *In re Steppan*, 394 F.2d 1013, 156 USPQ 143 (CCPA 1967). It is long established that a product may be adequately described as required under 35 U.S.C. § 112, by the method in which it is made. Method claims that recite the use of such products can be no less adequately described than method claims that take one material and make another.

Working examples of the subject matter of claims 155-157, 160 and 161, as well as the related claim 148 are provided by Example 4 in the specification. B6 spleen cells were stimulated with TAP-/- and RMA-S.B7-1 cells. TAP was directly ablated by knocking out gene expression in two independent ways. This stimulation of B6 cells reproducibly resulted in cytotoxic responses against RMA-S and TAP -/- targets. The example demonstrates that the response is sepcific to the novel endogenous self-antigen changes being expressed on the cells that have their TAP function altered. The reproducibility of the stimulation described in the example demonstrates that the claimed methods predictably produce cells having the recited properties.

Therefore, the Office's alleged basis for the rejection is not supported by fact or law, and the rejection should be withdrawn.